REMARKS

Amendments in the claims

Following entry of the present amendment, Claims 8-31 are pending. Claims 25-31 are withdrawn.

Claims 8, 9, 10, 26 and 27 are amended to further enhance clarity.

No new matter is introduced, and no change in inventorship is believed to result from any amendment herein.

RESPONSE TO OFFICE ACTION DATED 5 AUGUST 2009

1. Response to the Restriction Requirement

The Office Action notes that Groups II and III are rejoined (p. 2). Applicant provisionally elected Group I, Claims 8-24. In what appears to be a typographical error, the Office Action notes that Claims 1-8 are "examined herein insofar as they read on the elected invention…[and then in the next paragraph states] Claims 8-24 are examined herein." (p. 2) Since, Claims 1-7 were previously cancelled, and based on the remaining Office Action, the present response is made in the good faith assumption that the Office examined Claims 8-24 of provisionally elected Group I.

2. Rejection Under 35 U.S.C. §112, first paragraph

Claims 8-24 are rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enabling support in the specification. This rejection is respectfully traversed.

Claim 8 is directed to a method for prevention and/or treatment of a Parkinson's plus syndrome. The alleged lack of enablement applies to prevention of a Parkinson's plus syndrome, as treatment of a Parkinson's plus syndrome has been found enabled (Office Action, bridging p. 2-3).

The Examiner analyzes "prevention" of Parkinson's plus syndrome using the Wands factors (MPEP 2164.01(a)). Taking each of these factors in turn, Applicant responds as follows. In the interest of brevity, Applicant's references to rotigotine herein are intended to encompass rotigotine, a rotigotine salt or a rotigotine prodrug as recited in Claim 8.

Nature of the Invention: Applicant agrees that the present invention generally pertains to a method for the prevention and/or treatment of a Parkinson's plus syndrome.

The State of the Prior Art: The Examiner makes the following assertion:

> "The skilled artisan would view that the prevention of one or more symptoms of Parkinson's plus syndrome totally, absolutely, or permanently, [is] highly unlikely, since one cannot guarantee that the Parkinson's plus syndrome will always be prevented" (Office Action, p. 3).

First, this assertion is not supported by any evidence of record. Such a bold assertion can not be made without support. Second, even if one of ordinary skill in the art would find prevention of a Parkinson's plus syndrome "highly unlikely", Applicant's specification clearly teaches one of ordinary skill in the art that rotigotine demonstrates neuroprotective action. As set forth in Table 2 and Figures 1 and 2, "rotigotine had a neuroprotective action: on the one hand, the number of degenerating neurons in the mesencephalon was reduced following the administration of rotigotine (Table 2) and on the other the dopaminergic innervation of the striatum is virtually completely retained or restored (Figures 1 and 2)" (paragraph **[0019]**, emphasis added). The Examples in the specification teach that if rotigotine is administered, neuron loss can be stabilized. The result of such stability is that a clinical diagnosis of a Parkinson's plus syndrome (or early loss of pre- and postsynaptic dopaminergic neurons) is never made. Thus, although prior art may be limited on prevention of a Parkinson's plus syndrome, one of ordinary skill in the art reading Applicant's invention disclosure, would not find it "highly unlikely" that rotigotine can prevent a Parkinson's plus syndrome.

The Relative Skill of Those in the Art. Applicant agrees that the relative skill of those in the art is "very high."

Predictability of the Art: Applicant agrees with the implication in the Office Action (p. 4) that a method for prevention of a Parkinson's plus syndrome is a highly unpredictable art area. However, as fully articulated below (*see* "Guidance of the Specification" and "Working Examples"), the present specification is replete with guidance as to how preventive treatment can be practiced using rotigotine.

Guidance of the Specification: The statement that "no working examples are

presented in the specification as filed showing how to prevent Parkinson's plus syndrome" could hardly be more wrong. *See* Office Action, p. 4. Virtually the entire specification is directed to a method in which rotigotine or a salt or prodrug thereof is administered to a subject to treat and/or prevent a Parkinson's plus syndrome.

Specifically, the specification provides guidance as to administration of rotigotine (for example, paragraphs **[0060]-[0063]**) and dosages of rotigotine (for example, **[0064]-[0065]**). And thus, the specification provides ample guidance as to how to practice the invention.

Working Examples. Contrary to the Examiner's statement at p. 4, there are working examples in the specification which demonstrate prevention. The examples use the MPTP model, a model accepted in the art as predictive of neuroprotective properties of drugs (Dawson & Dawson (2002) Nature Neurosci. Suppl. 5:1058–1061). As discussed above, Figures 1 and 2 of the specification depict that dopaminergic innervation of the striatum is virtually completely retained or restored. Similarly, the specification (paragraph **[0023]**) reports findings from a study involving primates, which revealed, among other things, that "[t]he density of the nerve ending the in the striatum [of monkeys treated with MPTP] was much higher than it was in the untreated animals." The results show that rotigotine improved the survival of the neurons and the nerve endings in relation to the dose. Further, Example 4 (see paragraph **[0074]** of the specification as filed) shows that rotigotine was administered 16 hours before MPTP intoxication. Thus, the Examples provide rotigotine as ideally suited for preventing dopaminergic neuron loss in patients with a Parkinson's plus syndrome.

The specification accordingly, provides examples following well-established models, which sufficiently demonstrate preventive therapy using rotigotine.

Amount of Experimentation Necessary. Contrary to the Examiner's assertions in the passage bridging pp. 4-5, that the invention is directed to a combination and one of ordinary skill has to engage in undue experimentation to test the invention, Claims 8-24 are directed to a method and one of skill in the art does not need to engage in undue experimentation to prevent a Parkinson's plus syndrome using rotigotine. The specification lays out the claimed method, for example, how to administer rotigotine, the

suitable dosages of rotigotine, and other active substances that rotigotine can be combined with. *See*, the specification as filed, at paragraphs **[0060]-[0065]**. No undue amount of experimentation is necessary to practice the invention as presently claimed, based on the disclosure in the present specification.

In summary, a correct analysis of the *In re Wands* factors leads to the conclusion that, in addition to treatment, a method for prevention of a Parkinson's plus syndrome, as set forth in Claims 8-24, is fully enabled by the specification under 35 U.S.C. §112, first paragraph.

Withdrawal of the present rejection is respectfully requested.

3. Rejection under 35 U.S.C. §103(a) Over Rimpler In View of Mark

Claims 8, 11, 12, 14-18, and 21-24 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over US Patent Publication No. 2003/0166709 ("Rimpler") in view of Mark (2001) Movement Disorders 19:607-627 ("Mark"). This rejection is respectfully traversed.

3.1. Mark Demotivates One of Ordinary Skill in the Art From Using Rotigotine to Treat or Prevent a Parkinson's Plus Syndrome

The Examiner acknowledges on p. 7 that "Rimpler does not teach the disease associated with a dopamine-metabolic disorder as being Parkinson's plus syndrome." Therefore, the Examiner uses Mark as allegedly teaching

> "that typically methods of treatment that are used to treat Parkinson's disease are employed to reduce the symptoms of the above disorders [or Parkinson's plus syndrome]", and thus "[b]ased on the teaching on Mark, it is evident that said conditions are currently treated with agents that are used to treat Parkinson's disease." (Office Action, p. 7)

At the outset, the Examiner provides no citation for the allegation that Mark "teaches that typically methods of treatment that are used to treat Parkinson's disease are employed to reduce the symptoms of the above disorders." *See* Office Action, p. 7. Mark does not make such a broad conclusion nor can Mark be interpreted so broadly. Rather, Mark fails to report that dopamine agonists are therapeutically advantageous for any condition mentioned therein and, further, fails to mention rotigotine at all.

In fact, Mark teaches away from using dopamine agonists ("DA") for a Parkinson's plus syndrome for at least these three statements:

1. **DA avoidance**: "DLB [dementia with Lewy bodies] is a dopamine-deficiency disorder, [and] most patients should have some improvement in motor function with antiparkinsonian therapy, although patients who present with the cognitive syndrome may respond less well than *de novo* patients with typical PD", and that "dopamine agonists should be reduced, eliminated or avoided…[as] [a]ll dopamine agonists are tolerated less than levodopa, as dopaminergic agents have a high propensity for causing drug-induced psychosis" (p. 610, emphasis added);
2. **DA ineffectiveness**: For progressive supranuclear palsy "[d]opamine receptor agonists are almost always ineffective" (p. 616, emphasis added);
3. **DA resistance**: Cortical-basal ganglionic degeneration (p. 617-618) is decidedly refractory to treatment and no suggestion is provided regarding use of dopamine agonists.

Rimpler reports that rotigotine is a potent and selective dopamine D2 agonist. Accordingly, there is no motivation to combine a reference disclosing rotigotine as a dopamine agonist (Rimpler), and a reference that provides so much discouragement to use a dopamine agonist for treatment of a Parkinson's plus syndrome (Mark).

Thus, even if the combination of the references provides a method for treatment or prevention of a Parkinson's plus syndrome using rotigotine (which is not admitted herein), given the vast amount of teaching away, there is no rationale for a person of ordinary skill to select and modify elements from Rimpler and Mark to arrive at the present invention. *See KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (an obviousness inquiry includes determining whether there was an apparent reason to combine the known elements in the fashion claimed).

3.2 Treatment and Prevention of a Parkinson's Plus Syndrome With Rotigotine Is Unpredictable

Even if a rationale existed to select and modify elements from the cited documents (which is not admitted herein), the Examiner appears to be applying the

"obvious to try" standard in making the present rejection. This standard has been sanctioned by *KSR*, *supra*, but with the proviso that there has to be "a finite number of identified, predictable solutions" (emphasis added). Furthermore, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.*, emphasis added. As paraphrased in MPEP 2143.01.III, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis in original).

The Examiner acknowledges that "[t]he skilled artisan would view that the treatment to prevent a Parkinson's plus syndrome, absolutely, or permanently is highly unpredictable." (Office Action, p. 4, emphasis added) This is contrary to the Examiner's statement on p. 7 that "it would have been obvious to one of ordinary skill in that art, to at least try, with a reasonable degree of success, rotigotine for the treatment of Parkinson's plus syndrome." How could one of ordinary skill in the art have a reasonable degree of success for treating and preventing a Parkinson's plus syndrome given (1) such acknowledged unpredictability in the art, and (2) Mark's warning that dopamine agonists are not proven effective (or, in fact, are more harmful) in the treatment of dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and cortical-basal ganglionic degeneration? If anything, the existing art, such as Mark, leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success.

For at least the reasons presented above, a presumption of *prima facie* obviousness has not been established for Claim 8 over Rimpler in view of Mark.

Each of Claims 11, 12, 14-18, and 21-24 depends from and incorporates all limitations of Claim 8. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 11, 12, 14-18, and 21-24 is non-obvious over the cited art for at least the same reasons that Claim 8 is non-obvious.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over Rimpler in view of Mark is respectfully requested.

4. Rejection under 35 U.S.C. §103(a) Over Rimpler in View of Mark and In Further View of Lauterbach

Claim 13 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Rimpler in view of Mark and in further view of U.S. Patent Application Publication No. 2003/0026830 (herein "Lauterbach"). This rejection is respectfully traversed.

With respect to Claim 13, Rimpler and Mark are cited for their disclosures as summarized above. Lauterbach is cited for disclosures allegedly relevant to transdermal administration of rotigotine, which is a component in Claims 11 and 13. Claim 13 ultimately depends from Claim 8, which recites a method for prevention and/or treatment of a Parkinson's plus syndrome. Lauterbach provides no teaching or suggestion that corrects the deficiencies of Rimpler and Mark set forth above. In particular, Lauterbach would not motivate a person of ordinary skill to select rotigotine, as a method for prevention and/or treatment of a Parkinson's plus syndrome. Lauterbach does not contradict Mark's teaching away or change the unpredictability of Applicant's invention. For at least these reasons, Claim 13 is nonobvious over Rimpler in view of Mark and in further view of Lauterbach, as Claim 13 embodies all the limitations of Claim 8 from which it ultimately depends. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. MPEP 2143.03.

Reconsideration and withdrawal of the present rejection of Claim 13 under 35 USC § 103(a) over Rimpler in view of Mark and in further view of Lauterbach is respectfully requested.

5. Rejection under 35 U.S.C. §103(a) Over Rimpler In View of Mark and In Further View of Daas

Claims 19 and 20 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Rimpler in view of Mark and in further view of Den Daas *et al.*, J. Pharm. Pharmacol. 43:11–16 (1991) (herein "Daas"). This rejection is respectfully traversed.

With respect to Claims 19 and 20, Rimpler and Mark are cited for their disclosures as summarized above. Daas is cited for allegedly mentioning carbonate ester prodrugs of rotigotine. Claims 19 and 20 ultimately depend from Claim 8, which recites a method for prevention and/or treatment of a Parkinson's plus syndrome, including

administering rotigotine or a salt or prodrug thereof. Daas provides no teaching or suggestion that corrects the deficiencies of Rimpler and Mark set forth above. In particular, Daas would not motivate a person of ordinary skill to select rotigotine or a salt or prodrug thereof, as a method for prevention and/or treatment of a Parkinson's plus syndrome. Daas does not contradict Mark's teaching away or change the unpredictability of Applicant's invention. For at least these reasons, Claims 19 and 20 are nonobvious over Rimpler in view of Mark and in further view of Daas, as Claims 19 and 20 each embody all the limitations of Claim 8 from which they ultimately depend, and are therefore nonobvious for at least the same reasons that Claim 8 is nonobvious. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. MPEP 2143.03.

Reconsideration and withdrawal of the present rejection of Claims 19 and 20 under 35 USC § 103(a) under Rimpler in view of Mark and in further view of Daas is respectfully requested.

6. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.